IN THE SPECIFICATION

Paragraph beginning at Page 2, line 8

The present invention provides novel hydrate forms of alendronate sodium having water content of between 1.3 and 11.7 percent water. Typically, but without limitation, the present invention relates to the following novel hydrate forms ~~forms~~ of alendronate monosodium: 1/4 hydrate, 1/3 hydrate, hemihydrate, 2/3 hydrate, 3/4 hydrate, monohydrate, 5/4 hydrate. 4/3 hydrate, 3/2 hydrate, 5/3 hydrate, 7/4 hydrate and ~~dehydrate~~ dihydrate.

Paragraph beginning at Page 2, line 13

The present invention provides a new crystalline Form B of alendronate sodium, having a powder ~~x-ray~~ X-ray diffractogram substantially as depicted in Fig. 1a, with characteristic peaks at 12.2 ±0.2, 13.3 ±0.2, 14.8 ±0.2, 15.8 ±0.2, 16.3 ±0.2, 16.6 ±0.2, 17.2 ±0.2, 19.4 ±0.2, 21.3±0.2, 22.6 ±0.2, 23.2 ±0.2, 24.0 ±0.2, 25.2 ±0.2, 25.8 ±0.2, 27.4 ±0.2, 29.4 ±0.2, and 36.0±0.2 degrees 2 theta. Alendronate sodium Form B has significant IR bands as depicted in ~~Fig. 1b~~ Fig. 1c at 654 cm^{-1}, 955 cm^{-1}, 1074 cm-1, 1261 cm^{-1}, 1309 cm^{-1}, and 1614 cm^{-1}. The TGA curve, ~~Fig. 1c~~ Fig. 1b, shows a clear two-step loss on drying of 7.2%, which implies that the crystal form B contains a stoichiometric quantity of water close to that of the monohydrate (expected loss on drying value: 6.2%).

Paragraph beginning at Page 2, line 22

Another embodiment of the invention is a new crystalline Form D of alendronate sodium, having a powder X-ray diffractogram substantially as depicted in Fig. ~~4b~~ 4c has significant IR bands at 662 cm^{-1}, 919 cm^{-1}, 934 cm^{-1}, 954 cm^{-1}, 1054 cm^{-1}, 1072 cm^{-1} 1297 cm^{-1} and 1318 cm^{-1}. The TGA curve, as depicted in ~~Fig. 4c~~ Fig. 4b, shows a gradual loss on drying of ~~4.1~~ 3.7 % up to 180°C.

Paragraph beginning at Page 3, line 4

An additional embodiment is a new crystalline Form E of alendronate sodium, having a powder X-ray diffractogram substantially as depicted in FIG. 5a, with characteristic peaks at 7.0 ±0.2, 9.3 ±0.2, 11.8 ±0.2, 13.3 ±0.2, 14.0 ±0.2, 15.3 ±0.2, 16.2 ±0.2, 17.4 ±0.2, and 19.4 ±0.2 degrees 2 theta. Form E has significant IR bands as depicted in ~~Fig. 5b~~ Fig. 5c at 660 cm^{-1}, 897 cm^{-1}, 924 cm^{-1}, 953 cm^{-1}, 970 cm^{-1}, 1017 cm^{-1}, 1040 cm^{-1}, 1093 cm^{-1} ~~149~~ , 1149 cm^{-1}, 1177 cm^{-1}, 1252 cm^{-1} 1293 cm^{-1} 1337 cm^{-1}, 1535 cm^{-1}, 1606 cm^{-1}, and 1639 cm^{-1}. The TGA curve, as depicted in ~~Fig. 5c~~ Fig. 5b, shows a gradual loss on drying of ~~4.1~~ 3.7 % up to 150° C.

Paragraph beginning at Page 3, line 11

A still further embodiment of the invention is a new crystalline Form F of alendronate sodium, having a powder X-ray ~~diffractogram~~ diffractogram substantially as depicted in FIG. 6a, with characteristic peaks at 9.3 ±0.2, 11.7 ±0.2, 13.0 ±0.2,13.4 ±0.2, 14.2 ±0.2, 15.3 ±0.2, 16.2 ±0.2, 17.4 ±0.2, 19.1 ±0.2, 19.4 ±0.2 and 25.5 ±0.2 degrees 2 theta. Form F has significant IR bands as depicted in ~~Fig. 6b~~ Fig. 6c at 660 cm^{-1}, 893 cm^{-1}, 930 cm^{-1}, ~~9953~~ 953 cm^{-1}, 970 cm^{-1}, 982 cm^{-1}, 1010 cm^{-1}, 1033 cm^{-1} 1052 cm^{-1}, 1060 cm^{-1}, 1069 cm^{-1}, 1109 cm^{-1} and 1169 cm^{-1}, 1251 cm^{-1}, 1338 cm^{-1}, 1498 cm^{-1}, 1544 cm^{-1}, 1603 cm^{-1}, 1637 cm^{-1}, 1664 cm^{-1}. The TGA ~~Fig. 5c~~ Fig. 6b curve shows a gradual loss on drying of ~~4.1~~ 1.3 % up to 150°C.

Paragraph beginning at Page 3, line 19

A further embodiment is a new crystalline Form G of alendronate sodium, having a powder X-ray diffractogram substantially as depicted in FIG. 7a, with characteristic peaks at 9.5 ±0.2, 10.1 ±0.2, 12.7 ±0.2, 16.2 ±0.2, 17.3 ±0.2, 17.6 ±0.2, 19.1 ±0.2, 20.4 ±0.2, 20.9 ±0.2, 22.1 ±0.2, 24.8 ±0.2, 25.5 ±0.2, 28.0 ±0.2, 29.0 ±0.2, 29.6±0.2, 30.4 ±0.2, 32.4 ±0.2, and 32.8 ±0.2 degrees 2 theta. Form G has significant IR bands as depicted in ~~Fig. 7b~~ Fig. 7c at 665 cm^{-1}, 751 cm^{-1}, 856 cm^{-1}, 895 cm^{-1}, 913 cm^{-1}, 939 cm^{-1}, 1011 cm^{-1}, 1021 cm^{-1}, 1050 cm^{-1}, 1091 cm^{-1}, 1155 cm^{-1}, 1273 cm^{-1}, 1305 cm^{-1}, 1337 cm^{-1}, 1510 cm^{-1}, and 1639 cm^{-1} . The TGA curve, ~~Fig. 7c~~ Fig. 7b, shows a loss on drying of 6.5% which indicates that the crystal form G contains a stoichiometric quantity of water corresponding to that of the monohydrate (expected loss on drying value: 6.2%). This TGA step is sharp and occurs at 195°C. The relatively high temperature of dehydration implies that the water is bound tightly to the alendronate molecule. The dehydration step is immediately followed by another step due to decomposition. Due to the decomposition process that occurs adjacent to the dehydration, the conventional loss of drying method is not feasible, and for loss on drying determination the TGA is used.

Paragraph beginning at Page 4, line 7

Yet another embodiment is a new crystalline Form H of alendronate sodium, having a powder X-ray diffractogram substantially as depicted in FIG. 8a, with characteristic peaks at 9.2 ±0.2, 13.0 ±0.2, 14.2 ±0.2, 15.0 ±0.2, 17.1 ±0.2, 20.7 ±0.2, 22.0 ±0.2, 22.4 ±0.2, degrees two theta. Form H has significant IR bands, as depicted in ~~Fig. 8b~~ Fig. 8c, of 664 cm^{-1}, 688 cm^{-1}, 722 cm^{-1}, 751 cm^{-1}, 863 cm^{-1}, 893 cm^{-1}, 918 cm^{-1}, 936 cm^{-1}, 984 cm^{-1}, 1010 cm^{-1}, 1036 cm^{-1}, 1052 cm^{-1}, 1092 cm^{-1}, 1157 cm^{-1}, 1273 cm^{-1}, 1303 cm^{-1}, and 1338 cm^{-1}, 1499 cm^{-1}, 1598 cm^{-1}, 1636 cm^{-1}, and 1664 cm^{-1}. The TGA curve ~~Fig. 8c~~ Fig. 8b shows a sharp loss on drying of 3.7% at 170°C.

Paragraph beginning at Page 5, line 13

The invention further provides a new crystalline Form H of alendronate sodium, having a water content of 2.5% to ~~3.5~~ 3.7%.

Paragraph beginning at Page 5, line 15

The invention provides a new monohydrate and a new ~~dehydrate~~ dihydrate of alendronate sodium, having an X-ray diffractogram substantially as depicted in FIG. 2a and 3a, accordingly, with characteristic peaks at 9.3 ±0.2, 12.4 ±0.2, 13.5 ±0.2,17.1 ±0.2, 18.5±0.2, 19.7 ±0.2, 20.3 ±0.2, 21.0 ±0.2, 21.8 ±0.2, 23.4 ±0.2, 24.3 ±0.2, 24.9 ±0.2, 26.3±0.2, 30.0 ±0.2, and 34.4 ±0.2 degrees 2 theta. Form C as depicted in ~~Figs. 2b and 3b~~ Figs. 2c and 3c has significant IR bands at 660 cm^{-1}, 745 cm^{-1}, 865 cm–1, 913 cm^{-1} , 952 cm^{-1}, 966 cm^{-1}, 1017 cm^{-1} , 1046 cm^{-1}, 1128 cm^{-1}, 1174 cm^{-1}, 1235 cm^{-1}, 1340 cm^{-1}, 1402 cm^{-1}, 1544 cm^{-1}, 1606 cm^{-1}, and 1644 cm^{-1}. The TGA curve of the monohydrate Form C (~~Fig. 2c~~ Fig. 2b) shows a loss on drying of 5.6% which implies that the crystal Form C contains a stoichiometric quantity of water close to that of the monohydrate (expected loss on drying value: 6.2%). The TGA curve of the ~~dehydrate~~ dihydrate Form C (~~Fig. 3c~~ Fig. 3b) shows a sharp loss on drying of 12.0% which implies that the crystal Form C contains a stoichiometric quantity of water corresponding to ~~dehydrate~~ dihydrate (expected loss on drying value: 11.7%).

Paragraph beginning at Page 6, line 1

The present invention also relates to the method of preparing the compound 4-amino-1-hydroxybutylidene-1, 1-bisphosphonic acid monosodium salt having water content of 1.3% to 11.7% by reacting alendronic acid with one equivalent of sodium base in an aqueous organic solvent selected from the group consisting ~~of.~~ of acetone, DMSO, DMF, acetonitrile, alcohols, polyalcohols and/or their ethers, pyridine, sulfolane, –methyl pyrrolidinone and dioxane.

Paragraph beginning at Page 6, line 11

The invention further provides a method for making Form E of alendronate sodium, comprising treating alendronic acid, which is in anhydrous or monohydrate form, in a lower alkanol with ~~I~~ 1 equivalent of sodium base and 9 to 15 equivalents of water, followed by isolating the crystalline alendronate sodium Form E.

Paragraph beginning at Page 8, line 12

The invention further provides a method for making alendronate sodium ~~dehydrate~~ dihydrate comprising treating crystalline alendronate sodium trihydrate with an effective amount of drying agent followed by isolating the crystalline alendronate sodium ~~dehydrate~~ dihydrate.

Paragraph beginning at Page 8, line 19

The invention further provides a method for making alendronate sodium monohydrate comprising treating crystalline alendronate sodium ~~dehydrate~~ dihydrate with a sufficient amount of drying agent followed by isolating the crystalline alendronate sodium monohydrate.

Paragraph beginning at Page 9, line 8

FIGS. 3a, 3b, and 3c show, respectively, the powder X-ray diffraction spectrum, the thermograviometric (TGA) curve and the infrared spectrum of alendronate sodium ~~dehydrate~~ dihydrate Form C.

Paragraph beginning at Page 9, line13

FIGS. 5a, 5b, and 5c show, respectively, the powder X-ray diffraction spectrum, the ~~(~~thermograviometric (TGA) curve~~)~~ and the infrared spectrum of alendronate sodium Form E.

Paragraph beginning at Page 10, line 16

Those skilled in the art will appreciate that the term ~~monohydrate"~~ "monohydrate" when used in reference to alendronic acid describes a crystalline material having a water content of 6.7%. Those skilled in the art will also understand that the term "anhydrous" when used in reference to alendronic acid describes alendronic acid that is substantially free of water.

Paragraph beginning at Page 10, line 23

One skilled in the art will also appreciate that the term "~~dehydrate~~ dihydrate" when used in reference to the monosodium salt of alendronic acid describes a crystalline material having a water content of approximately 11.7%.

Paragraph beginning at Page 13, line 11

In accordance with the aspects of this invention wherein alendronate sodium trihydrate (Form C) is converted to alendronate sodium ~~dehydrate~~ dihydrate (Form C), alendronate sodium trihydrate as prepared by methods known in the art is

added to an alkanol which is substantially free of water, preferably absolute ethanol. This mixture is treated with a drying agent, preferably by refluxing the mixture in a reflux condenser wherein the condensate formed passes through 3Å molecular sieves. The weight:weight ratio of molecular sieves to alendronate sodium trihydrate is preferably about 2:1 and most preferably 12:5. Refluxing of the mixture is preferably done for 24 hours with stirring. Alendronate sodium ~~dehydrate~~ dihydrate is then isolated, preferably by filtration after cooling to ambient temperature, washing with absolute ether and drying overnight in a vacuum oven at ambient temperature and at a pressure of 10 mm to 15 mm of mercury.

Paragraph beginning at Page 15, line 1

The thermogravimetric curves were obtained by methods known in the art using a Mettler TGA TG50. The weight of the samples was about 10 mg. The temperature range was from 25°C to at least 200°C, at the rate of 10°C/min. Samples were purged with ~~nitrogen~~ nitrogen gas at a flow rate of 40 ml/min. Standard 150 ml aluminum crucibles were used.

Paragraph beginning at Page 16, line 4

A 250 ml flask was fitted with a mechanical stirrer, a thermometer, and a reflux condenser. The flask was charged with 41.1 ml of a solution of sodium hydroxide in ethanol (0.49N, 20.1 mmol), 8.9 ml of ethanol, water (0 to 40 mol. eq., according to the crystal form desired), and 5g (20.1 mmol) of anhydrous alendronic acid. The reaction mixture was boiled with vigorous stirring for about 15 hours until the ~~of~~ pH of the liquid phase remained constant (approx. pH 7). After cooling of the reaction mixture to ambient temperature, the solid material was filtered, washed with absolute ethanol, and dried overnight in a vacuum oven (10-15mmHg, ambient temperature) to give 96-99% sodium alendronate having the following crystal forms: crystal Form D, when 0-4 (preferably 0-2) mol. eq. water were used; crystal Form F, when 5-8 (preferably 6-7) mol. eq. water were used; crystal Form E, when 9-15 (preferably 12) mol. eq. water were used; and crystal Form G, when 15-40 (preferably 25-35) mol. eq. water were used. The monosodium salt was confirmed by atomic absorption and by measuring the pH of a 0.5% aqueous solution of the salt (approx. pH 4.4).

Paragraph beginning at Page 17, line 12

A one liter flask was fitted with a magnetic bar stirrer, Soxhlet extraction funnel (operating volume 150 ml) charged with 3Å molecular sieves (60 g), and reflux condenser connected to a drying tube with 3Å molecular sieves. The flask was charged with sodium alendronate trihydrate (25 g) and absolute ethanol (450 ml, vol.% of water <

0.1%). The mixture was boiled with stirring for 24 hours. After cooling to ambient temperature the solid material was filtered, washed with absolute ethyl ether, and dried overnight in a vacuum oven (10-15 mm Hg, ambient temperature) to give sodium alendronate ~~dehydrate~~ dihydrate.

Heading beginning at Page 19, line 15

Preparation of ~~Alendronate~~ Alendronate Sodium Form G from Alendronic Acid Monohydrate

Paragraph beginning at Page 19, line 22

A one liter flask was fitted with a mechanical stirrer, a thermometer, and a ~~reflux.~~ reflux condenser. The flask was charged with alendronic acid monohydrate (25 g, 0.094 mol) and aqueous ethanol. The mixture was heated to boiling with stirring. The aqueous ethanolic sodium hydroxide was added dropwise to the suspension of alendronic acid monohydrate in aqueous ethanol for 3 hours at reflux with vigorously stirring. Then the mixture was stirred at reflux for additional 15 hours. The mixture was cooled to room temperature with stirring. The solid was filtered, washed with absolute ethanol, and dried overnight in a vacuum oven (10-15 mm Hg, 40-50°C) to give 26.2g of alendronate sodium, having crystalline Form G.